

DOCKET NO.: JANB-0002/JAB-1442

Application No.: 09/868,535

Amendment accompanying RCE

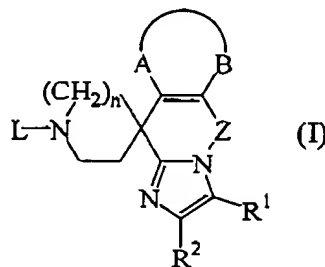
PATENT

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

Claims 1-15 (canceled).

16. (currently amended) A compound of formula



or a N-oxide, an addition salt, a quaternary amine or a stereochemically isomeric form thereof wherein

R¹ is hydrogen, C₁₋₆alkyl, halo, formyl, carboxyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylcarbonyl,

N(R³R⁴)C(=O)-, N(R³R⁴)C(=O)N(R⁵)-, ethenyl substituted with carboxyl or C₁₋

₆alkyloxycarbonyl, or C₁₋₆alkyl substituted with hydroxy, carboxyl, C₁₋₆alkyloxy,

C₁₋₆alkyloxycarbonyl, N(R³R⁴)C(=O)-, C₁₋₆alkylC(=O)N(R⁵)-, C₁₋₆alkylS(=O)₂N(R⁵)- or

N(R³R⁴)C(=O)N(R⁵)-;

wherein each R³ and each R⁴ independently are hydrogen or C₁₋₄alkyl;

R⁵ is hydrogen or hydroxy;

R² is hydrogen, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, N(R³R⁴)C(=O)-, aryl or

halo;

n is 1 or 2;

-A-B- represents a bivalent radical of formula

-Y-CH=CH- (a-1);

-CH=CH-Y- (a-2); or

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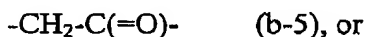
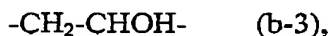
wherein each hydrogen atom in the radicals (a-1) to (a-3) may independently be replaced by

R^6 wherein R^6 is selected from C_{1-6} alkyl, halo, hydroxy, C_{1-6} alkyloxy, ethenyl substituted with carboxyl or C_{1-6} alkyloxycarbonyl, hydroxy C_{1-6} alkyl, formyl, carboxyl or hydroxycarbonyl C_{1-6} alkyl;

each Y independently is a bivalent radical of formula -O-, -S- or -NR⁷-;

wherein R^7 is hydrogen, C_{1-6} alkyl or C_{1-6} alkylcarbonyl;

Z is a bivalent radical of formula

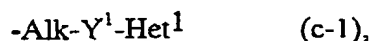


with the proviso that the bivalent radicals (b-3), (b-4), (b-5) and (b-6) are connected to the nitrogen of the imidazole ring via their -CH₂- moiety;

wherein p is 1, 2, 3 or 4;

L is hydrogen; C_{1-6} alkyl; C_{2-6} alkenyl; C_{1-6} alkylcarbonyl; C_{1-6} alkyloxycarbonyl; C_{1-6} alkyl substituted with one or more substituents each independently selected from hydroxy, carboxyl, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, aryl, aryloxy, cyano or $R^8\text{HN-}$ wherein R^8 is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl, or C_{1-6} alkylcarbonyl; or

L represents a radical of formula



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$$-\text{Alk}-\text{NH}-\text{CO}-\text{Het}^2 \quad (\text{c-2}) \text{ or}$$
$$-\text{Alk}-\text{Het}^3 \quad (\text{c-3}) ; \text{ wherein}$$
Alk represents C_{1-4} alkanediyl; Y^1 represents O, S or NH;

Het¹ and Het² each represent furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C_{1-4} alkyl substituents; pyrrolyl or pyrazolyl optionally substituted with formyl, hydroxy C_{1-4} alkyl, hydroxycarbonyl, C_{1-4} alkyloxycarbonyl or with one or two C_{1-4} alkyl substituents; thiadiazolyl or oxadiazolyl optionally substituted with amino or C_{1-4} alkyl; pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C_{1-4} alkyl, C_{1-4} alkyloxy, amino, hydroxy or halo; and

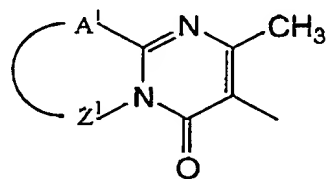
Het³ represents furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C_{1-4} alkyl substituents; pyrrolyl or pyrazolyl optionally substituted with formyl, hydroxy C_{1-4} alkyl, hydroxycarbonyl, C_{1-4} alkyloxycarbonyl or with one or two C_{1-4} alkyl substituents; thiadiazolyl or oxadiazolyl optionally substituted with amino or C_{1-4} alkyl; pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C_{1-4} alkyl, C_{1-4} alkyloxy, amino, hydroxy, halo, 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C_{1-4} alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula

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wherein

A^1-Z^1 represents $S-CH=CH$, $S-CH_2-CH_2$, $S-CH_2-CH_2-CH_2$, $CH=CH-CH=CH$,

or $CH_2-CH_2-CH_2-CH_2$;

aryl is phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, C_{1-4} alkyl, polyhalo C_{1-4} alkyl, cyano, aminocarbonyl, C_{1-4} alkyloxy or polyhalo C_{1-4} alkyloxy;

with the proviso that 5,6-dihydrospiro[imidazo[1,2-b][3]benzazepine-11[11H],4'-piperidine] and pharmaceutically acceptable addition salts thereof ~~are not included~~, and 6,11-dihydro-1'-(phenylmethyl)-5H-spiro[imidazo[1,2-b][3]benzazepine-11,4'-piperidine] (*E*)-2-butenedioate(1:2) and pharmaceutically acceptable addition salts thereof is are not included.

17. (previously presented) A compound according to claim 16 wherein L is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl or C_{1-6} alkyl substituted with hydroxy, carboxyl, C_{1-6} alkyloxy or C_{1-6} alkyloxycarbonyl.

18. (previously presented) A compound according to claim 16 wherein L is C_{1-6} alkyl substituted with aryl and C_{1-6} alkyloxycarbonyl.

19. (previously presented) A compound according to claim 16 wherein -A-B- is a bivalent radical of formula $-CH=CH-CH=CH-$ (a-3) or $-CH=CH-Y-$ (a-2).

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20. (previously presented) A compound according to claim 16 wherein Z is $-(CH_2)_p-$ (b-1), $-CH=CH-$ (b-2), or $-CH_2-O-$ (b-4).
21. (previously presented) A compound according to claim 16, wherein L is hydrogen, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, carboxy C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl, or C_{1-6} alkyloxycarbonyl C_{1-6} alkyl.
22. (previously presented) A compound according to claim 16 wherein R^1 is hydroxy C_{1-6} alkyl, formyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyloxy C_{1-6} alkyl, $N(R^3R^4)C(=O)-$, halo or hydrogen.
23. (previously presented) A compound according to claim 16 wherein the compound is
- 5,6-dihydrospiro[11H-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-carboxamide dihydrochloride;
- 1'-butyl-5,6-dihydrospiro[imidazo[2,1-b][3]benzazepine-11-[11H],4'-piperidine];
- 6,11-dihydro-1'-methylspiro[5H-imidazo[2,1-b][3]benzazepine-11,4'-piperidine] cyclohexylsulfamate(1:2);
- 6,11-dihydrospiro[5-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-methanol (E)-2-butenedioate (2:1);
- 3-chloro-6,11-dihydrospiro[5H-imidazo[2,1-b][3]benzazepine-11,4'-piperidine] (E)-2-butenedioate (1:1);
- 6,11-dihydro-3-(methoxymethyl)spiro[5H-imidazo[2,1-b][3]benzazepine-11,4'-piperidine] (E)-2-butenedioate (1:1);

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6,11-dihydro-1'-(2-hydroxyethyl)spiro[5H-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-carboxamide;

6,11-dihydro-1'-methylspiro[5H-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-3-carboxamide monohydrate;

ethyl 3-(aminocarbonyl)-6,11-dihydro- α -phenylspiro[5H-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-1'-propanoate monohydrochloride;

3-(aminocarbonyl)-6,11-dihydrospiro[5H-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-1'-carboxylate;

spiro[10H-imidazo[1,2-a]thieno[3,2-d]azepine-10,4'-piperidine];

6,11-dihydrospiro[5H-imidazo[2,1-b][3]benzazepine-11,4'-piperidine]-2,3-dicarboxamide dihydrochloride monohydrate; or

a N-oxide, an addition salt, a quaternary amine or a stereochemically isomeric form thereof.

24. (previously presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as defined in claim 16.

25. (previously presented) A process of preparing a pharmaceutical composition, comprising mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound as defined in claim 16.

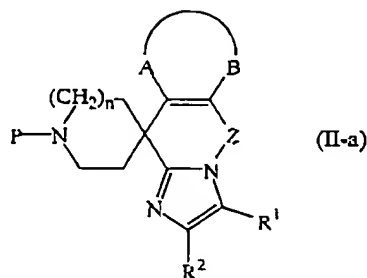
26. (currently amended) A compound of formula

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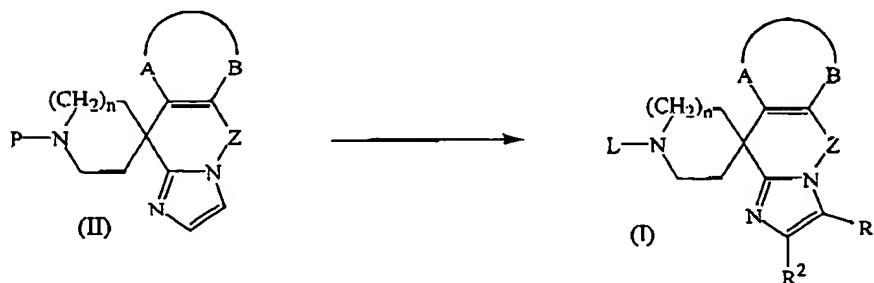
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or a *N*-oxide, an addition salt, a quaternary amine or a stereochemically isomeric form thereof wherein P is a protective group and n, -A-B-, Z, R¹ and R² are defined as in claim 16, with the proviso that 6,11-dihydro-1'-(phenylmethyl)-5*H*-spiro[imidazo[1,2-b][3]-benzazepine-11,4'-piperidine] (*E*)-2-butenedioate(1:2) and pharmaceutically acceptable addition salts thereof is are not included.

27. (previously presented) A compound according to claim 26 wherein P is benzyl.
28. (previously presented) A process of preparing a compound as claimed in claim 16, comprising
- a) deprotecting an intermediate of formula (II), followed optionally by derivatizing either the piperidine moiety, or the imidazole moiety, or both the piperidine moiety and the imidazole moiety



with P being a protective group;

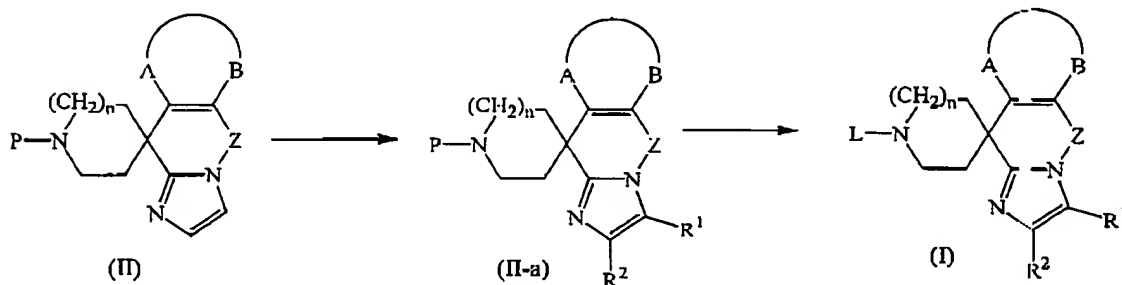
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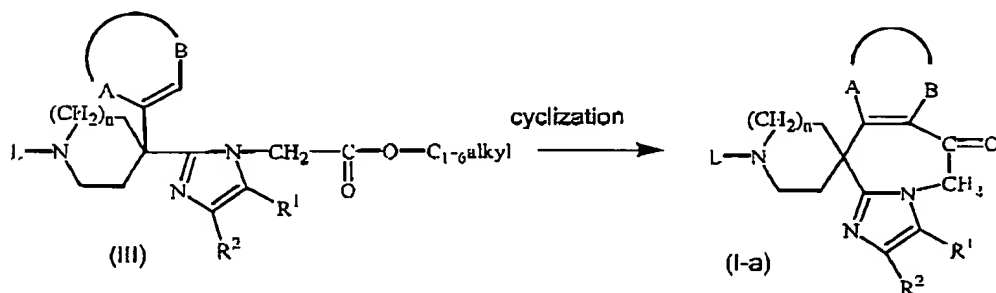
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- b) derivatizing an intermediate of formula (II) at the imidazole moiety, to form an intermediate of formula (II-a), followed by deprotecting the piperidine moiety, and followed optionally by derivatizing the piperidine moiety



- c) cyclizing an intermediate of formula (III) in the presence of an appropriate acid, to form a compound of formula (I-a)



and, optionally, converting compounds of formula (I) and (I-a) into each other, and further, optionally, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, optionally, preparing stereochemically isomeric forms or N-oxide forms thereof.

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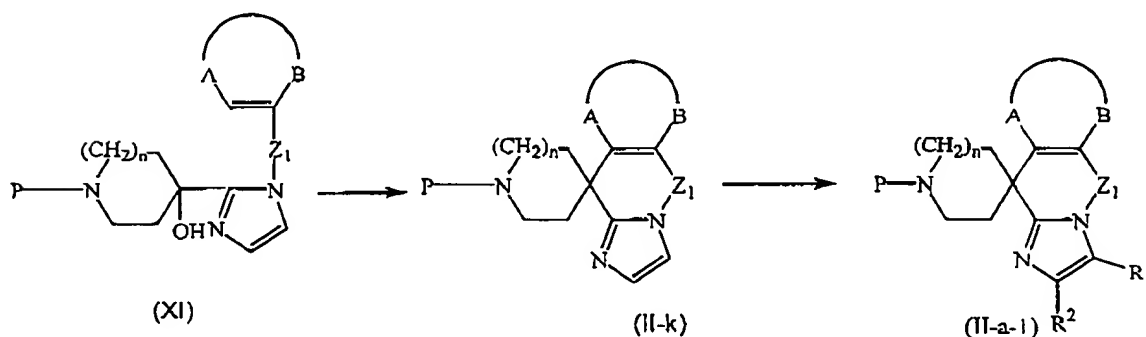
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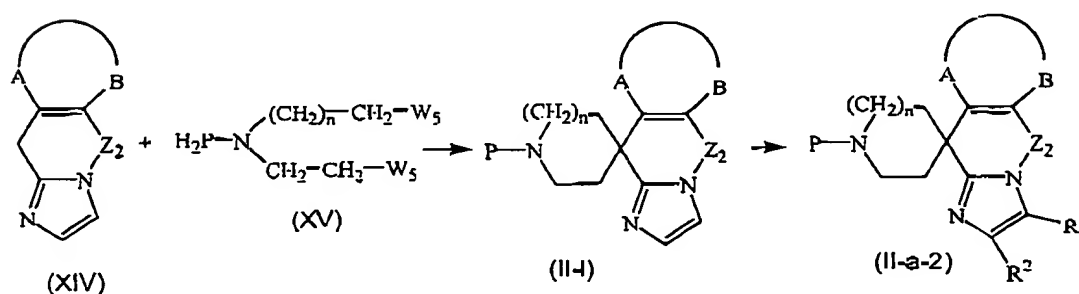
29. (previously presented) A process of preparing a compound as claimed in claim 27, comprising,

- a) cyclizing a compound of formula (XI) with an appropriate acid, to form a compound of formula (II-k), followed optionally by derivatizing the imidazole moiety, to form a compound of formula (II-a-1)



with Z_1 being a bivalent radical of formula $-(CH_2)_p-$, wherein p is 1,2,3 or 4; and

- b) reacting a tricyclic moiety of formula (XIV) with a reagent of formula (XV) under an inert atmosphere in a reaction inert solvent in the presence of a suitable base, to form a compound of formula (II-l), followed optionally by derivatizing the imidazole moiety to form a compound of formula (II-a-2)



with W_5 being a suitable leaving group, and Z_2 being a bivalent radical of formula

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$-(CH_2)_p-$, or $-CH_2-O-$, wherein p is 1,2,3 or 4.

30. (previously presented) A method of treating a subject suffering from allergic disease, comprising administering to said subject a therapeutically effective amount of a compound as defined in claim 16.